A CONSIDERATION OF POSSIBLE TOXIC AND NERVOUS FACTORS IN THE PRODUCTION OF TRAUMATIC SHOCK

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In discussing a condition so complex as traumatic shock, and so beset by theories, we shall do well to start with a review of the generally accepted facts. The facts which I shall recite will refer, for the present, to delayed shock, the usual form, which becomes evident some hours after a severe injury.

Primary and Secondary Phenomena in Shock.—The phenomena of shock may be separated into a primary phenomenon and those which are secondary and subordinate. If the primary condition is present it explains the secondary, because the secondary conditions are the natural results of the primary. The central problem, therefore, is that of defining the primary feature and explaining it.

The obvious primary feature of shock is the low arterial pressure. Clinical and experimental observations have shown that the systolic pressure may fall to approximately eighty millimetres of mercury and still maintain an adequate blood flow if the individual remains quiet. When the pressure falls below a critical level of seventy-five or eighty millimetres of mercury and remains below that general level for an hour or more, certain secondary phenomena begin to appear, such as reduction of the basal metabolic rate and a lessening of the alkali reserve due to appearance of non-volatile metabolites.[1] These effects naturally follow when, because the arterial pressure drops below the critical level, the rate of blood flow is diminished to such a degree that the oxygen delivery is insufficient for tissue needs. In addition, sweating occurs, the skin is cold and may have a dusky appearance, the fingernails are bluish, the pulse is thready, the heart beats rapidly, the respiration shallow and feeble is occasionally interrupted by sighs, thirst is prominent but the taking of fluid is likely to cause vomiting, and the patient, with pale lips and an apathetic look, is usually weak and toneless. Consideration of these secondary phenomena, however, need not detain us now.

The Cause of the Low Blood-pressure of Shock.—What is the explanation of the primary feature of shock, the low blood-pressure? On this problem the numerous theories of shock have centred. Three factors may be concerned: (*a*) a weakened vigor of the heart; (*b*) a lessening of vasomotor tone so that the capacity of the vascular system is greater than its content and the blood is therefore not held under normal tension; and (*c*) the obverse of this, a reduction of blood volume below the minimal capacity of the vascular system so that again the capacity is greater than the content.

The evidence at hand indicates that certainly in the early stages of shock, though the blood-pressure may have been low for a considerable period, the heart is not seriously damaged. Repeated observations made during the War on lower animals and on human beings, in whom a state of shock was present, proved that when the volume of circulating fluid is increased and the arterial pressure is raised, even rather abruptly, the heart does not fail because of the extra work thereby imposed but takes up the task with adequate power.[2] The ability of the heart to meet increased demands, although it has been subjected for some time to an inadequate volume flow of blood through its vessels because of lowered blood-pressure, is wholly in harmony with other evidence of the resilience of cardiac muscle. The testimony is quite definite that weakness and lack of vigor of the heart are rarely, if ever, the occasion for the low blood-pressure of the shock-state.

The second factor, loss of vasomotor tone, has played a prominent rôle in the theorizing and experimenting of investigators who have concerned themselves with the explanation of shock. No doubt the shutting-off of vasoconstrictor impulses, as, for example, in high transection of the spinal cord or in high spinal anæthesia, increases the capacity of the circulatory system so that it no longer fits tightly around the contained blood. Thereupon the vascular system neither returns the blood to the heart in normal volume nor presents to the blood discharged from the heart the usual peripheral resistance. The arterial pressure, naturally, is reduced. Although the vasomotor centre in shock has been assumed to be "exhausted" and although the low pressure has been ascribed to such exhaustion, there is much evidence against it. Among the medullary centres, for example, that governing vasoconstriction is well known to be especially resistant to such unfavorable conditions as lessened blood supply. There are numerous observations, also, which prove that in the early stages of shock, when the blood-pressure is falling, the peripheral vessels are, because of reflexes from the carotid sinus, constricted instead of being relaxed; that even in the late stages of shock the centre can respond with greater activity when stimulated by afferent impulses; and that the supposed pooling of blood in the capacious splanchnic area, because of loss of vascular tone, is a myth. As already noted, a prolonged low blood-pressure is attended by a deficient supply of oxygen to the tissues. Undoubtedly nerve cells are peculiarly sensitive to lack of oxygen, and therefore persistence of the state of shock may result ultimately in a loss of vasomotor tone. The morphological changes which have been emphasized as indicating exhaustion of nerve cells are quite reasonably explained by persistent relative anæmia.

The remaining factor to be considered in explaining delayed shock is that of reduced blood volume—a reduction below the minimal capacity of the blood vessels, *i.e.*, below the ability of the neurovascular system to contract further and press upon the small quantity of blood that is left. There is abundant evidence that in delayed shock the blood volume may be greatly

reduced. In clinical studies carried on by Keith[3] during the War the reduction ranged from 15 to nearly 50 per cent. An analysis of his cases showed that if the drop was less than 20 per cent., the systolic pressure remained above 100 millimetres of mercury and the condition might be compensated for by passage of fluid into the vessels from the tissues; that when the drop ranged between 25 and 35 per cent. the blood-pressure was usually between seventy and eighty millimetres and the condition was worse, with the patients pale, restless, thirsty and vomiting; and that when the drop was more than 35 per cent. the pressure might be as low as sixty millimetres and the outlook was then extremely serious. Keith's observations relating a low blood-pressure to a reduced blood volume correspond roughly to earlier studies and estimates made by Robertson and Bock.[4] In experimental shock, likewise, Gasser, Erlanger and Meek[5] noted that however the state was induced the quantity of circulating blood was decreased. The reduction was not observed solely in extreme shock, but began to appear soon after the shock-inducing procedure was started. In some animals the typical low pressure developed when the blood volume was lessened not more than 17 per cent. From all the foregoing evidence the conclusion is reasonable that reduction of blood volume is the immediate factor in establishing the low blood-pressure of delayed shock. The next question to be answered is directed toward learning of possible conditions which may diminish the quantity of circulating blood.

Modes of Reducing Blood Volume.—Hæmorrhage is, of course, the simplest and most direct way of reducing the blood volume. The resemblance between traumatic shock and the results of serious hæmorrhage led older observers to remark that "Hæmorrhage is shock and shock, hæmorrhage." Although there are minor differences between the two conditions, that statement is surprisingly coincident with the evidence now in hand. The striking effect of hæmorrhage, even when slight, in augmenting the state of shock emphasizes the close relation between reduction of blood volume by hæmorrhage and reduction by some other condition or conditions.

Traumatic Toxæmia.—During the War much emphasis was laid upon a supposed toxic factor as a means of reducing the blood volume. As a rule the observations did not extend to an actual study of the quantity of the circulating blood, but merely went so far as to suggest a relation between a possible toxic factor and the state of shock. Both French and English clinical observers reported that shock was associated with extensive damage to tissues and with multiple wounds scattered over the body. Even under these circumstances shock did not come on promptly but only after delay. It was noted that when conditions were favorable to absorption from a damaged area, as, for example, when the traumatized region communicated with the surface by only a small orifice, shock was likely to develop. Furthermore, Quénu[6] and others found that any means employed to delay or check absorption from the injured part delayed or prevented the development of shock—for example, a tourniquet was protective when used to separate a crushed foot from the

rest of the body. Removal of the tourniquet, on the contrary, was followed after some hours by an onset of the shock state. Finally, suppression of the injured region, if not too long delayed, caused shock to disappear. Thus cutting away the damaged tissue by débridement, or even tying a tourniquet around a limb so badly smashed that amputation seemed inevitable, was followed, as noted by McNee and his associates,[7] by rapid and maintained improvement. In support of these observations was evidence adduced by Bayliss and myself[8] that pointed to a toxic factor in shock experimentally induced in cats. We reported experiments in which tissue damage resulted, first, in a gradual and finally persistent lowering of arterial pressure; second, in a recovery of pressure when the injured region was isolated from the rest of the body; and finally, in a failure of the pressure to fall so long as the vessels to the injured region were blocked. These results were regarded as analogous to the hypotensive effects produced by tissue extracts when injected intravenously and were specifically attributed at the time to a possible liberation from the damaged structures of substance having a histamine-like action, for Dale and others (see [2], p. 152) had shown that histamine occurs in tissues and that when injected in minute amounts it has quite remarkable effects in reducing the amount of circulating blood and in lowering blood-pressure.

Our observations were confirmed by Cornioley and Kotzareff[9] in experiments on guinea-pigs and rabbits whose blood, they declared, became toxic to normal animals, and by McIver and Haggart[10] who induced shock in a second cat by crossed circulation from a cat in which tissues were damaged, and also by Freed[11] who has reported that moderate tissue injury produces definite and usually fatal shock in rats deprived of their adrenal glands but does not have that effect in normal rats. Other observers, however, have adduced considerable experimental evidence against the theory of traumatic toxæmia. Thus Thorpe[12] has found that skeletal muscles contain an exceedingly small amount of histamine (a supposed cause of the low pressure)—a much smaller proportion than in any other tissues examined. Smith[13] and also Parsons and Phemister[14] were unable to demonstrate any toxic substance carried by the blood-stream from an injured area, or derived from damaged muscles; and they attributed the fall of blood-pressure, in such experiments as Bayliss and I performed, to extravasation into smashed tissues. Likewise, Blalock, Beard and Johnson[15] estimated that in dogs the loss of blood and fluid into the traumatized region and its neighborhood is sufficient to account for the reduction of blood volume. Bayliss and I did not overlook that possibility; but our conclusion after comparing in cats the weights of injured and uninjured limbs, symmetrically excised, was that the segregated blood did not explain the incidence of shock. Finally, Simonart,[16] although confirming the onset of shock after muscle damage, inferred that the fall of pressure was caused by afferent impulses from the swollen parts, because it did not occur in his animals if afferent nerves had been cut—a result contradictory to my own observations and those of Parsons and Phemister.

The experiments just cited are certainly unfavorable to the idea that a

toxic factor is operating in the production of shock. It may be pertinent to suggest, however, that discrepancies between results obtained by Bayliss and myself in 1917–1918 and those obtained by later experimenters should not be taken as disproving the possibility of a traumatic toxæmia. We were using war-time animals, often ill-nourished derelicts, in which shock was produced with exceptional ease. Moreover, we were working on cats, an animal which, in my experience, succumbs to severe injury much more readily than the dog, the animal chiefly employed by most recent investigators. But such differences would have minor significance if there were direct, convincing, positive evidence that a vasodepressive toxin derived from dying tissues induces shock, or if, on the other hand, there were good proof that such toxic material could not exist. The positive evidence is lacking. It is opposed by negative evidence. Meanwhile, we have long known that tissue extracts when injected cause a fall of blood-pressure; we have learned that histamine, or a substance acting like it, is present in considerable amount in some structures of the body, and, as Dale, Laidlaw and Richards[17] showed, causes conditions closely resembling wound shock; and recently we have heard from the biochemists that when muscles, for example, are damaged and are disintegrating, adenosine and its natural complex, adenylic acid, are set free and may have marked vasodepressive influence as well as inducing a leucocytosis. And even though we may not have devised experiments which demonstrate the presence of any shock-inducing chemical agent, there still remains the clinical testimony, mentioned above, that material absorbed from dead and dying tissues and distributed in the organism may be toxic—so toxic as to play a rôle in lessening the quantity of circulating blood. It seems unwarranted, therefore, to exclude from further consideration the view that traumatic shock may be, at least in part, a resultant of toxæmia.

Evidence for a Nervous Factor.—It must be admitted that the emphasis laid on a possible toxic cause of wound shock, and also the supposition that any nervous agency must operate quickly, resulted in a failure to consider certain conditions which were universally admitted to be contributory to the development of the shock state. Thus, continued pain, prolonged exposure to cold, persistent fear and other great emotional excitement, and likewise restlessness, were all recognized as favorable to the induction of shock.

Every one of the above-mentioned conditions involves special activity of the nervous system, and particularly the sympatho-adrenal apparatus. In looking back over experiences with seriously wounded men during the War, one is struck by the failure of observers to pay proper attention to the effects which might be produced by these nervous factors. Such factors had been suggested years before. In 1909, Malcolm[18] put forth the view that in shock the arteries are over-contracted and assumed that the lessened capacity of the circulatory system would press the plasma out of the vessels into the tissues. He failed to account, however, for the primary vasoconstriction on which he based his argument. In experimental shock, likewise, Seelig and his collaborators[19] reported definite evidence that in shocked animals the blood-

vessels are clamped down on their contents. Also Erlanger and his associates[20] called attention to the fact that in all types of experimental shock which they studied vasoconstriction was present; indeed, they suggested that the causative factor was the "reduced circulation brought about possibly through the action of pain stimuli, and of a certain amount of hemorrhage, on the vasoconstrictor mechanism." In support of this view, Erlanger and Gasser[21] demonstrated that a decrease in the quantity of the circulating blood could be produced by injecting rather large doses of adrenalin continuously for periods lasting nearly a half hour. They did not succeed, however, "either by direct or reflex stimulation of the vasoconstrictor center in inducing in animals a peripheral constriction of the duration that was necessary, in their experience with other methods, to start the animal on the road to shock." It is to the credit of Norman Freeman[22] that he perceived that not only pain but also the other factors (exposure to cold, great emotional excitement, asphyxia and hæmorrhage) recognized as contributory to the shock state, or likely to aggravate it if present, have one physiological action in common —they are all effective in evoking hyperactivity of the sympatho-adrenal system[23] and thereby causing, except in the heart and in skeletal muscles, a pronounced and extensive vasoconstriction.

The problem which confronted Freeman was that of determining the effects on blood volume of prolonged sympatho-adrenal hyperactivity. As a means of provoking such prolonged effects, I suggested the use of an animal manifesting sham rage. In 1925, Britton and I[24] had reported that if under brief ether anæsthesia the cerebral cortex is swiftly destroyed, the cat, on recovering from the ether, will display to a supreme degree the physiological phenomena of rage, with lashing of the tail, protrusion of the claws, tugging at the thongs, dilation of the pupils, erection of the hairs of the back and tail, pouring out of sweat on toe pads, increase of blood sugar, rapid heart rate, rise of blood-pressure, and greatly increased secretion of adrenine. The sympatho-adrenal system, in short, is stimulated in a natural manner continuously and excessively for two or three hours, until the animal succumbs. The central question to be settled was whether this lasting display of unusual sympatho-adrenal function is associated with a decrease in the amount of circulating blood.

Careful tests of blood volume demonstrated that the spontaneous emotional activity of the pseudaffective state does in fact result in a fall in the blood volume. In fifteen experiments the fall averaged approximately 22 per cent. Not only was there a decrease of the fluid elements, but the corpuscular elements of the blood were likewise segregated from the general circulation. It is of interest that Freeman* succeeded also in bringing about a lowering of the blood volume as much as 27 per cent. by injecting adrenalin continuously for about two hours, at the physiological rate of the output from the adrenal

* A still unpublished critical examination, by Gregersen, of methods for determining plasma volume in successive tests has shown that it would be reasonable to increase Freeman's estimates between 10 and 20 per cent.

glands in response to "painful" (*i.e.*, afferent) stimulation. Ergotoxine is known to block the vasoconstrictor effects of both adrenine and sympathetic nerve impulses. Experiments demonstrated that after ergotoxine neither the injection of adrenalin nor sham rage caused a decrease of blood volume; in spite of all possible evidences of the presence of the pseudaffective state, such as extrusion of claws, panting, and lashing of the tail, the quantity of circulating blood was not lessened. The conclusion was justified, therefore, that sympatho-adrenal stimulation was responsible for the phenomenon.

Another test proving that hyperactivity of the sympatho-adrenal system was the primary condition for bringing about the reduced amount of blood in currency and the consequent lowered blood-pressure was performed on completely sympathectomized animals. Here again, although the signs of sham rage were persistently present so far as they could be in an animal without the sympathetic system, the blood volume failed to fall. Furthermore, at the end of five hours the blood-pressure was still maintained at its original level, whereas usually, when the sympatho-adrenal system was present, the blood-pressure dropped to a shock level within two or three hours, as the blood volume decreased. Finally, the significant observation was made by Freeman that prolonged vasodilation and low arterial tension, caused by continuously stimulating the depressor nerve, does not decrease the quantity of blood in the vessels.

In the experiments reported by Freeman the area of traumatized tissue within the brain was largely excluded from contact with flowing blood because the carotid arteries were tied. Traumatic toxæmia, therefore, was a minimal factor if present at all. The absence of reduction of blood volume in completely sympathectomized animals manifesting sham rage indicates, likewise, that a toxic factor was not operative. Furthermore, the experiments are not to be explained by local loss of blood or fluid into the traumatized area. There was no injury of the tissues whatever in the experiments with prolonged injection of adrenalin, and the trauma in the experiments with sham rage was solely in the cranial cavity where swelling of the tissues is definitely limited. Also, the damage done to the brain in the sympathectomized animals was essentially the same as that in the normal animals, and yet the blood volume was not reduced. Neither a toxic factor, therefore, nor a hæmorrhagic factor, was present. The explanation offered by Freeman for the drop in blood volume was an increased capillary permeability resulting from more or less asphyxia[25] due to prolonged contraction of the arterioles, especially in parts of the body (*e.g.*, the skin and the gastro-intestinal tract) where vasoconstriction is prominent. This might cause a concentration and probably a stagnation of the corpuscles in the capillaries. The dusky appearance of the skin, the bluish fingernails, the high corpuscular counts in superficial areas (commonly observed in wounded men during the War),[26] and the clogging of the capillaries of the intestinal villi, noted by Erlanger and his collaborators in experimental shock, would thus receive a plausible explanation.

While causing splanchnic and cutaneous vasoconstriction, however, the sympatho-adrenal system induces also dilation of the blood-vessels of skeletal muscles,[27] where the capillary bed, as Krogh[28] has shown, may be enormously increased by the opening of closed channels. Ordinarily the redistribution of blood thus effected is associated with an outpouring of fluid through capillary walls to spaces between the muscle fibres. But ordinarily it is associated also with such muscular activity as would pump this fluid onward into lymphatics which would return it to the general circulation. In early stages of shock relaxed arterioles in muscles would result in a greater filtration pressure in the recipient capillaries, and this would naturally lead to the passage of fluid from the blood to the perivascular intermuscular spaces. At the same time, because of absence of considerable bodily movement in injured men, the fluid would be left there instead of being restored to currency. Thus the blood volume might actually be more reduced by greater filtration into muscles, where vessels are unduly dilated, than in the skin and viscera, where vessels are unduly constricted. In late stages of shock, when the blood volume has been reduced, the increased capacity of the dilated vascular area in muscles, which remain idle, might play a significant part in the diminishing return of blood to the heart. It is of interest to note that Starling[29] also has suggested, for other reasons, a segregation of blood in the muscles. The possibility of explaining thus the whereabouts of the elusive "lost blood" of shock obviously calls for further observations.

The view that excessive and prolonged sympatho-adrenal activity may produce shock by reducing blood volume may explain certain mysterious conditions which have been baffling. I have in mind instances of death because of great fear or because of horrifying experiences. Cuthbert Wallace,[30] who had large acquaintance with war wounds, has written of cases of shock in which the initial injury was comparatively trivial or even negligible. He mentions specifically two wounded men whose cases came to his attention. "One was buried by the explosion of a shell in a cellar, the other was blown up by a buried shell over which he had lighted a fire. Both exhibited all the classic symptoms of shock, which lasted over forty-eight hours; in both treatment was of no avail. In neither did the post-mortem examination show any gross lesion." Explanation of such cases is difficult in other than terms involving the activity of the nervous system.

As mentioned above, emotional excitement is only one of the conditions which may induce extra activity of the sympatho-adrenal system. Pain, cold, asphyxia, hæmorrhage, and low blood-pressure itself have the same effect. Manifestly these states are often present at the same time and therefore would coöperate in producing shock. It is known, furthermore, that as the blood-pressure falls in the shock state and the organism reacts to diminishing pressure by increasing vasoconstriction, there is, to be sure, a continuance of the blood flow in the heart and central nervous system, but at the same time a gradually reduced flow elsewhere. Gesell[31] found that a loss of about 10 per cent. of the estimated blood in the body lowered the flow in the submaxillary

gland, for example, by 60 per cent. Thus a vicious circle is started which, unless interrupted, is sure to render the state of the circulation progressively worse because of the progressive further reduction in the blood volume that ensues.

During the War, recognition of the fact that shock is due to lowered quantity of blood in circulation led to transfusion as a means of treatment. If the rôle of prolonged activity of the sympatho-adrenal system in reducing blood volume is admitted, the evidence is clear that transfusion would, in a quite reasonable manner, break into the vicious circle which is established by the low blood-pressure, for it would lessen the constriction of the vessels and also the consequent shock-producing anæmia of the tissues. As transfusion would set aside one of the coöperating conditions favorable to the incidence or continuance of shock, warmth would set aside another, *i.e.,* the influence of cold in causing vasoconstriction. The efficacy of moderate warmth in the treatment of shock was abundantly illustrated in War experience. Still another point made reasonable by the view that excessive activity of the sympatho-adrenal system may produce or augment shock is the early use of morphine to lessen pain, fear and restlessness. All three conditions are associated with increase of sympatho-adrenal function, and therefore contribute to establishing a state which reduces the volume of circulating blood—and morphine helps to set them aside.

The foregoing survey of recent developments of ideas concerning shock emphasizes the importance of recognizing the involvement of and possible coöperation of various factors which may produce it. I still believe that a toxic factor may operate in certain conditions, and it seems highly probable also that there are nervous factors—a possible inhibition of vasoconstrictors and stimulation of vasodilators in acute circulatory collapse, and more certainly a prolonged activity of the sympatho-adrenal system when conditions are present which bring that system into operation. In delayed shock, whether due to a toxic factor or to a lasting vascular spasm, or both, the result is a reduced blood volume. In either state, of course, hæmorrhage plays an accessory rôle, for thereby the blood volume is reduced by direct loss; and circumstances which cause discharge of body fluid in sweat, or lead to water deprivation for a long period, are indirect contributors to the same end.

I trust that no one will assume that any attempt is here made to say a final word on the problem presented by traumatic shock. We have had it with us for many decades, and we may have it with us always. Perhaps we should not be so pessimistic, however, but should have faith that efforts to learn the truth, even though they may be rather blind and groping and indecisive, will prove to have been helpful in reaching the final solution.

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